Modulation of resting-state connectivity and working memory in adults with high schizotypal characteristics
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Introduction
- Individuals with high schizotypal characteristics exhibit signs that are related to core symptoms of schizophrenia patients.
- Ideas of self-reference
- Excessive social anxiety
- Odd beliefs
- Unusual perceptual experiences
- Cognitive deficits such as impairment in working memory have been shown to represent a major aspect of schizophrenia symptomatology (Orellana & Slachcinsky, 2013).
- Altered interaction between default-mode network (DMN) and the executive control / Frontal-parietal network (FPN) has been found in schizophrenia patients (Whitfield-Gabrieli et al., 2009).
- SEP-363856 is a novel non-D2 mechanism of action compound, which is currently being studied in Phase 2 clinical trials as a treatment for patients with schizophrenia. Possible targets include agonism of 5-HT1A and TAAR1 receptors.

Phase 1, Randomized double-blinded, placebo-controlled, single dose study (ClinicalTrials.gov Identifier: NCT01972711)
- How does the candidate antipsychotic, SEP-363856, modulates the interaction between DMN and FPN?
- Is resting-state brain connectivity related to working memory?

Design and Procedure

1. Screening (N = 133)
   Schizotypal Personality Questionnaire (SPQ):
   - Low: score < 10
   - High: score ≥ 40

2. fMRI data collection
   - NBack task
   - Resting state

3. Treatment
   - Amisulpride (400 mg)
   - SEP-363856 (50 mg)
   - Placebo

N = 16 18 17 15 17 17
Gender (M/F) 2.2 1.6 1.4 0.9 1.1 0.7
SPQ 53.8 2.9 49.8 3.5 53.8 3.4
IQ 113.4 116.3 111.6 116.1 113.9 118.0
PNASS 36.1 31.8 40.0 31.6 39.6 31.2

Nback:
- 0-Back
- 1-Back
- 2-Back
- 3-Back

SOA = 2 s, ISI = 1.5 s, blocked design, 10 stimuli per block, 16 blocks

Resting State fMRI Acquisition:
37 ascending axial slices, 3.5 mm isotropic voxels, TR = 2s, TE = 30ms, FOV 224 × 224 mm2, flip angle = 75°, 180 volumes, 6.1 min.

Summary: Individuals with high schizotypal showed decreased performance in the low-load conditions, when treated with either SEP-363856 and Amisulpride. However, in the highest-demand condition, Amisulpride facilitated working memory performance across both schizotypal groups.

Relationship between Working memory and rsfMRI

Summary: Better Nback performance is associated with greater PCC-DLPFC anti-correlation, but only in the SEP-treated group.

Conclusion
- SEP-363856 showed specific effect on enhancing the anti-correlation between DMN and FPN in healthy adults with high schizotypal characteristics.
- Cognitive performance in working memory tasks benefits from the enhanced anti-correlation modulated by SEP-363856.